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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUNDGREN, JEFFREY S	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/893,878	LADNER ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *20-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-19 are pending in the instant application; claims 20-25 have been withdrawn from consideration.

Election of Invention

Applicant's election with traverse of Group I, claims 1-19, in the reply filed on July 2, 2004, is acknowledged. Applicants allege that Group II should be rejoined with Group I because Group II depends on Group I.

Whether or not there is any merit to Applicants' arguments, Applicants have indicated the status of claims 20-25 as "withdrawn," but failed to comply with 37 C.F.R. § 1.121(c), and have omitted the text of the claims.

However, regardless of being "dependent" as alleged by Applicants, the key issue in determining whether or not a restriction is proper is whether the inventions are: 1) distinct *and* 2) present a serious burden to search and examine. Neither of these issues has been addressed by Applicants. For this reason, the Restriction Requirement is deemed proper, and therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 is indefinite because it is unclear how a protein domain may differ from another protein domain prior to the construction of the DNA that expresses the protein, *i.e.*, putting the protein sequence before the DNA sequence.

Claim 19 is indefinite for reciting the phrase "a portion thereof functional to direct said display," because it is not clear what protein sequences would constitute the claimed portion.

Double Patenting

An obvious-type double patenting rejection is appropriate when the conflicting claims are not identical, but an Examiner finds an application claim is not patentably distinct from the reference claims because the examined claim is either anticipate by, or would have been obvious over the reference claim(s). See, *e.g.*, *In re Berg*, 14 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Claim 1 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,223,409, in view of Nayak *et al.*, U.S. Patent No. 4,752,473, issued on June 21, 1988.

The primary difference between instant claim 1 and the subject matter claimed in the '409 patent is the use of the eukaryotic cells for the surface display (the claims in the '409 patent are directed to phage display).

Nayak teaches a method for producing heterologous proteins on the surface of yeast through the use of a protein coding DNA sequence coding for a protein and a signal peptide:

> "Sequence analysis of HA of influenza virus A indicates that the polypeptide consists of a hydrophobic signal peptide at the amino terminus of the molecule and another hydrophobic region of 24-27 amino acids at the carboxyl terminus (36, 49, 50). In mammalian cells, the full length HA is expressed, glycosylated and exported to the cell surface (5, 7, 51, 52). It is believed that the HA made in yeast is processed the same way as in the eukaryotic cells and therefore it is probably membrane associated. Immunoprecipitation of various fractions of the cells harboring the plasmid pWYHAC51 was performed. Both mechanical and enzymatic fractionation procedures were employed to analyze the localization of the hemagglutinin.
>
> From the above tests, the HA appears to be predominantly localized in the membrane of the yeast cells. However, mechanical breaking of the cells does not clearly fractionate the HA into membrane or cytosolic fractions even though in the membrane fraction, there seems to be more HA present than in the soluble fraction, considering the amount of radioactivity put on

> the gels. On the other hand, the enzymatic separation clearly identifies the hemagglutinin in the membrane since no or little HA is detected in the cytoplasmic or periplasmic fractions. These observations indicate that the hemagglutinin made in yeast is processed in a manner similar to one that occurs in higher eukaryotic systems. Therefore, it shows that the glycosylation sites on the HA are recognized by the yeast glycosylation system in a manner similar to that of higher eukaryotic organisms. The expected glycosylation sites on the yeast expressed HA are therefore expected to be the same as those mentioned in the Background of the Invention."

Nayak, at col. 7, lines 47 through col. 8 line 12.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the '409 patent claims and Nayak are directed to the surface display of chimeric/heterologous proteins. One of ordinary skill in the art would have been motivated by the teaching of Nayak for using yeast for producing the protein library of the '409 patent because of the large surface area and concentration of library members found using yeast. Therefore, the invention as a whole is prima facie obvious at the time it was invented.

Claims 1-3, 5, 6, 10-12, 16, and 19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,979,538, in view of Nayak *et al.*, U.S. Patent No. 4,752,473, issued on June 21, 1988.

The primary difference between instant claim 1 and the subject matter claimed in the '538 patent is the use of the eukaryotic cells for the surface display (the claims in the '538 patent are directed to phage display).

Claim 17 of the '538 patent is directed to the method of claim 1 in which the potential binding domains are each at least 88% identical to a naturally occurring antibody variable domain at amino acid positions which do not correspond to the hypervariable region of the naturally occurring antibody variable domain, as supported by the definition and requirements of the chains in the specification; accordingly this claim as defined is generic to the instant claims 2, 3, 5, 6, 10-12. Claim 19 requires that there be at least a portion of an outer surface protein.

Nayak teaches a method for producing heterologous proteins on the surface of yeast through the use of a protein coding DNA sequence coding for a protein and a signal peptide wherein the signal peptide is at least a portion of an outer surface protein:

> "Sequence analysis of HA of influenza virus A indicates that the polypeptide consists of a hydrophobic signal peptide at the amino terminus of the molecule and another hydrophobic region of 24-27 amino acids at the carboxyl terminus (36, 49, 50). In mammalian cells, the full length HA is expressed, glycosylated and exported to the cell surface (5, 7, 51, 52). It is believed that the HA made in yeast is processed the same way as in the eukaryotic cells and therefore it is probably membrane associated. Immunoprecipitation of various fractions of the cells harboring the plasmid pWYHAC51 was performed. Both mechanical and enzymatic fractionation procedures were employed to analyze the localization of the hemagglutinin.
>
> From the above tests, the HA appears to be predominantly localized in the membrane of the yeast cells. However, mechanical breaking of the cells does not clearly fractionate the HA into membrane or cytosolic fractions even though in the membrane fraction, there seems to be more HA present than in the soluble fraction, considering the amount of radioactivity put on the gels. On the other hand, the enzymatic separation clearly identifies the hemagglutinin in the membrane since no or little HA is detected in the cytoplasmic or periplasmic fractions. These observations indicate that the hemagglutinin made in yeast is processed in a manner similar to one that occurs in higher eukaryotic systems. Therefore, it shows that the glycosylation sites on the HA are recognized by the yeast glycosylation system in a manner similar to that of higher eukaryotic organisms. The expected glycosylation sites on the yeast expressed HA are therefore expected to be the same as those mentioned in the Background of the Invention."

Nayak, at col. 7, lines 47 through col. 8 line 12. Nayak also teaches subcloning (see Fig. 1 and description thereof), as required by claim 16 of the instant application.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the '538 patent claims and Nayak are directed to the surface display of chimeric/heterologous proteins. One of ordinary skill in the art would have been motivated by the teaching of Nayak for using yeast for producing the protein library of the '538 patent because of the large surface area and concentration of library members

found using yeast. Therefore, the invention as a whole is prima facie obvious at the time it was invented.

Claims 1-3, 5, 6, 10-12, 16, 17 and 19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,979,538, in view of Nayak *et al.*, U.S. Patent No. 4,752,473, issued on June 21, 1988, in further view of Huston *et al.*, *PNAS USA 85*:5879-5883 (**1988**).

The limitations of the claims in the '538 patent, the teachings of Nayak, and the application to the instant claims 1-3, 5, 6, 10-12, 16, and 19 above, is hereby incorporated into the instant rejection.

Claims 4 and 7 are directed to the method wherein the binding protein is a single chain antibody; claims 8 and 9 are directed to methods wherein the binding domains are Fab fragments of an antibody. Claims 13-15 are directed to certain amounts of variation within the binding domains.

Neither the claims in the '538 patent not the teachings of Nayak are directed to, or teach, these aforementioned limitations.

Huston teaches the construction of an Fv analogue in which both heavy- and light-chain variable domains (VH and VL) were part of a single polypeptide chain. Synthetic genes for the 26-10 anti-digoxin VH and VL regions were designed to permit their connection through a linker segment, as well as other manipulations. The synthetic gene for single-chain Fv (sFv) was expressed in Escherichia coli as a fusion protein, from which the sFv protein was isolated. The sFv was renatured with recovery of binding specificity and affinity similar to those of the parent molecule. Thus, variable domains connected artificially to form one polypeptide chain can be renatured into properly folded Fv regions. Huston teaches:

> "Binding site variants of 26-10 sFv may likewise be constructed (13), or its entire framework replaced, while keeping complementarity determining region sequences unchanged (12). The immunopharmacology of biosynthetic antibody binding sites could prove particularly interesting, insofar as their small size may accelerate the pharmacokinetics and reduce the immunogenicity observed for ***Fab fragments*** administered intravenously (48). Further research on the ***single-chain Fv*** and related

> immunoconjugates may lead to biomedical applications that have been heretofore impossible with conventional antibody fragments."

Huston, at page 5883, col. 1.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the '538 patent claims and Nayak are directed to the surface display of chimeric/heterologous proteins, and further by the teachings of Huston for producing binding member of scFvs and Fabs. One of ordinary skill in the art would have been motivated by the teaching of Nayak for using yeast for producing the protein library of the '538 patent because of the large surface area and concentration of library members found using yeast, and the teachings of Huston for the development of immonlogics compounds. Regarding the degree/amount of variation in the binding domains, such limitations are considered obvious in view of the prior art as a routine optimization of a range. See *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969), where the claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions. Therefore, the invention as a whole is prima facie obvious at the time it was invented.

Claims 1-3, 5, 6, 10-12, 16, 17 and 19, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,979,538, in view of Nayak *et al.*, U.S. Patent No. 4,752,473, issued on June 21, 1988, in further view of Murray *et al.*, U.S. Patent No. 4,769,328, issued on September 6, 1988, and/or Sharon *et al.*, *PNAS USA 83*:2628-2631 (**1986**).

The limitations of the claims in the '538 patent, the teachings of Nayak, and the application to the instant claims 1-3, 5, 6, 10-12, 16, and 19 above, is hereby incorporated into the instant rejection. However, it is noted that neither claim/teach a DNA synthesizer, or DNA synthesis as required by claim 17.

Murray teaches biologically active PDGF analogs that are expressed in yeast. The analogs are produced by yeast strains transformed with an extrachromosomal element composed

of a strong transcriptional promoter directing the expression of a gene which encodes a protein having substantially the same biological activity as PDGF. Murray states:

> "To precisely remove codons 1-66 of v-sis, oligonucleotide directed mutagenesis was performed essentially according to the two primer method of Zoller (Zoller, et al., Manual for Advanced Techniques in Molecular Cloning Course, Cold Spring Harbor Laboratory, 1983). Oligonucleotide ZC 130 3' AGAAACCTATTTTCCTCGGACCCA 5' was synthesized on an Applied Biosystems 380-A DNA synthesizer. Fifty pmoles of ZC 130 were kinased in 10 ul of kinase buffer (BRL) with 4 units of T_4 polynucleotide kinase for 45 minutes at 37° C. The enzyme was inactivated by heating at 65° C for 10 minutes."

Murray, at Example V.

Sharon teaches the mutation of antibodies, and the construction of the mutants using a DNA synthesizer (page 2628, paragraph bridging col. 1 and 2)

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the '538 patent claims and Nayak are directed to the surface display of chimeric/heterologous proteins. One of ordinary skill in the art would have been motivated by the teaching of Nayak for using yeast for producing the protein library of the '538 patent because of the large surface area and concentration of library members found using yeast. One of ordinary skill in the art would have further recognized the advantages of using a DNA synthesizer for creating mutations in a nucleic acid for use in a vector as a means of preparing a non-naturally occurring nucleotide source, as taught by Murray and/or Sharon. Therefore, the invention as a whole is prima facie obvious at the time it was invented.

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should

Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

JON EPPERSON, PH.D.
PATENT EXAMINER